TFW

Patent Application
Attorney Docket No.PC25240A

I hereby certify that this correspondence is being deposited with the United States Postal Service as first-class mail in an envelope addressed to: P.O. Box 1450, Alexandria, VA 22313 on this 8th day of March, 2005.

By Mary C. Bickel
(Signature of person mailing)
Mary C. Bickel
(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Timothy A. Hagen, et al.

APPLICATION NO.: 10/763,340 : Examiner: Thurman Page

FILING DATE: January 23, 2004 : Group Art Unit: 1615

TITLE: AZITHROMYCIN DOSAGE FORMS WITH REDUCED SIDE EFFECTS

Hon. Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450
ATTN: Technology Center Special Program Examiner

Sir:

PETITION TO MAKE SPECIAL UNDER 37 C.F.R. § 1.102

Applicants hereby request that the present application be made special for accelerated examination under 37 C.F.R. § 1.102 and M.P.E.P. § 708.02 (VIII).

REQUIREMENT OF M.P.E.P. § 708.02 (VIII)(A) - FEE

The commissioner is authorized to charge the fee set forth in 37 C.F.R. 1.17(h) in the amount of $130.00 to our Deposit Account No. 16-1445 for consideration of the present petition. Therefore, Applicants have satisfied the requirement of M.P.E.P. § 708.02 (VIII)(A).

REQUIREMENT OF M.P.E.P. § 708.02 (VIII)(B) – SINGLE INVENTION

Applicants have concurrently filed a Preliminary Amendment to present a set of amended claims. Applicants believe that such amended claims in the Preliminary Amendment are directed to a single invention. However, if the Patent Office determines that all the claims presented are not obviously directed to a single invention, Applicants will make an election without traverse. Applicants respectfully submit that the requirements of M.P.E.P. § 708.02 (VIII)(B) have been met.

REQUIREMENT OF M.P.E.P. § 708.02 (VIII)(C) – PRE-EXAMINATION SEARCH

M.P.E.P. § 708.02 (VIII)(C) requires the submission of a statement on pre-examination search. Applicants note that such requirement can be met by a search made by a foreign patent office if the claims in the corresponding foreign application are of the same or similar scope to the claims in the U.S. application for which special status is requested.

Applicants would like to point out that a search was made by the International Searching Authority/European Patent Office and the claims in the PCT application are of similar scope to the

claims in the present U.S. application. For your convenience, a copy of the pending PCT claims is enclosed as well as copies of the PCT search report and the written opinion. Therefore, Applicants have satisfied the requirement of M.P.E.P. § 708.02 (VIII)(C).

REQUIREMENT OF M.P.E.P. § 708.02 (VIII)(D) – COPIES OF THE REFERENCES

The PCT search report cited the following six references:

D1 EP 0679400A (Pfizer) 2 November 1995;

D2 US 5633006A (Catania Joseph et al.) 27 May 1997;

D3 US 6068859;

D4 WO03/063838A (Pfizer Product Inc. (US)), 7 August 2003;

D5 WO03/053399 (Pfizer), 3 July 2003; and

EP0298650A.

References D2, D3 and the U.S. counterpart of reference D1 (U.S.P.No. 5,605,889) were cited/submitted to the U.S. Patent Office in an Information Disclosure Statement mailed on June 18, 2004. The U.S. counterparts of D4 (U.S. Patent Application Publication No. 2003228357), D5 (U.S. Patent Application Publication No. 2003190365) and EP0298650 (U.S. Patent No. 6,268,489) were also cited/submitted to the U.S. Patent Office in a Supplemental Information Disclosure Statement mailed on February 24, 2005. Therefore, the requirement of M.P.E.P. § 708.02 (VIII)(D) was satisfied, as these references were already cited/submitted to the Patent Office.

REQUIREMENT OF M.P.E.P. § 708.02 (VIII)(D) – DETAILED DISCUSSIONS

The references cited in the PCT search report were discussed in detail in the enclosed PCT written opinion. Specifically, the PCT written opinion stated that the PCT claims 6-20, 22, 23, 25-29, 31-38 are novel over references D1-D5. In addition, Applicants have amended the U.S. claims to scopes similar to those of the PCT claims 6-20, 22, 23, 25-29, 31-38. Therefore, Applicants have satisfied the requirement of M.P.E.P. § 708.02 (VIII)(D).

CONCLUSION

Applicants respectfully submit that the present petition has satisfied all the requirements of M.P.E.P. § 708.02 (VIII)(A), (B), (C), (D) and (E). Accordingly favorable consideration of the present petition is respectfully requested.

It is believed that no fee, other than the $130 fee set forth in 37 C.F.R. 1.17(h) is deemed necessary in connection with the filing of the present petition. However, if any other fees are required, the Commissioner is hereby authorized to charge any such fees to our Deposit Account No. 16-1445.

Respectfully submitted,

Date: March 8, 2005

Lance Liu

Lance Y. Liu
Attorney for Applicant(s)
Reg. No. 45,379

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Pfizer Inc.
Patent Department, MS 8260-1611
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Attorney Docket No. PC25240A-PCT
International Application No. PCT/IB2004/001654
International Filing Date: 14.05.2004

Claims

We claim:

1. An oral dosage form of azithromycin, comprising:
   a) azithromycin; and
   b) an effective amount of an alkalizing agent.

2. An oral dosage form of Claim 1 wherein the alkalizing agent further comprises an aluminum salt, a magnesium salt, a calcium salt, a bicarbonate, a phosphate, a metal hydroxide, a metal oxide, N-methyl glucamine, arginine, an arginine salt, an amine, or a combination thereof.

3. An oral dosage form of Claims 1-2 wherein said azithromycin comprises an immediate release form of azithromycin.

4. An oral dosage form of Claims 1-2 wherein said azithromycin comprises a sustained release form of azithromycin.

5. An oral dosage form of Claims 1-2 wherein said azithromycin comprises azithromycin multiparticulates wherein said azithromycin multiparticulates further comprise:
   (a) azithromycin; and
   (b) a pharmaceutically acceptable carrier.

6. An oral dosage form of Claim 5 wherein said carrier is a wax, a glyceride or a mixture thereof.

7. An oral dosage form of Claim 6 wherein said glyceride comprises a mixture of glyceryl monobehenate, glyceryl dibehenate and glyceryl tribehenate.

8. An oral dosage form of Claim 6 further comprising a dissolution enhancer.

9. An oral dosage form of Claim 8 wherein said dissolution enhancer

comprises a surfactant selected from the group consisting of poloxamers, docusate salts, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, sorbitan esters, alkyl sulfates, polysorbates and polyoxyethylene alkyl esters.

10. An oral dosage form comprising:

(a) an effective amount of an alkalizing agent; and

(b) multiparticulates wherein said multiparticulates comprise

(i) azithromycin,

(ii) a mixture of glyceryl monobehenate, glyceryl dibehenate and glyceryl tribehenate, and

(iii) a poloxamer.

11. An oral dosage form of Claim 10 wherein the poloxamer comprises poloxamer 407.

12. An oral dosage form of Claim 11 wherein the alkalizing agent comprises tribasic sodium phosphate.

13. An oral dosage form of Claim 12 wherein the alkalizing agent further comprises magnesium hydroxide.

14. An oral dosage form of Claims 1, 2, 10-13 further comprising about 250 mgA to about 7 gA of azithromycin.

15. An oral dosage form of Claim 14 further comprising 1.8 to 2.2 gA of azithromycin.

16. An azithromycin oral dosage form, comprising:

(a) at least about 200 mg of tribasic sodium phosphate;

(b) At least about 100 mg of magnesium hydroxide, and

(c) multiparticulates, wherein said multiparticulates comprise

(i) azithromycin,

(ii) a mixture of glyceryl monobehenate, glyceryl dibehenate and glyceryl tribehenate, and

(iii) poloxamer 407,

and wherein said dosage form contains about 1.5 gA to about 4 gA of azithromycin.

17. An oral dosage form of Claim 16, further comprising:

(a) 300 mg to 400 mg of tribasic sodium phosphate; and

(b) 200 mg to 300 mg of magnesium hydroxide.

18. An oral dosage form of Claim 17 further comprising 1.8 to 2.2 gA of azithromycin.

19. An oral dosage form of Claims 1-2, 10-13, and 16-8 wherein said azithromycin is azithromycin dihydrate.

20. An oral dosage form of Claims 1, 2, 10-13 and 16-18 wherein said azithromycin is at least 70 wt% crystalline.

21. A method for reducing the frequency of gastrointestinal side effects, associated with administering azithromycin to a human, comprising contiguously administering azithromycin and an effective amount of alkalizing agent to said human wherein the frequency of gastrointestinal side effects is reduced as compared to the frequency experienced when administering an equal dose of azithromycin without said alkalizing agent.

22. A method of treating a bacterial or protozoal infection in a human in need thereof comprising contiguously administering to said human azithromycin and an effective amount of an alkalizing agent.

23. A method of Claims 21-22 further comprising administering between about 250 mgA and about 7 gA of azithromycin to said human.

24. A method of Claim 23 wherein the azithromycin is administered in a single dose.

25. A method of Claim 24 further comprising administering between about 1.5 and about 4 gA of azithromycin.

26. A method of Claim 24 further comprising administering between 1.8 and 2.2 gA of azithromycin to said human in a single dose.

27. A method of Claims 21-22 further comprising administering between 30 mgA/kg and 90 mgA /kg of azithromycin to a human, wherein said human is a child weighing 30 kg or less.

28. A method of Claim 27 wherein the azithromycin is administered in a single dose.

29. A method of Claim 28 further comprising administering between 45 mgA/kg and 75 mgA /kg of azithromycin to a child weighing 30 kg or less.

30. A method of Claims 21-22 wherein said azithromycin comprises azithromycin multiparticulates wherein said azithromycin multiparticulates further comprise:

(a) azithromycin; and

(b) a pharmaceutically acceptable carrier.

31. A method of Claim 30 wherein said carrier comprises a mixture of glyceryl monobehenate, glyceryl dibehenate and glyceryl tribehenate.

32. A method of Claim 30 wherein said azithromycin multiparticulates further comprise a dissolution enhancer.

33. A method of Claim 32 wherein said dissolution enhancer comprises a surfactant selected from the group consisting of poloxamers, docusate salts,

polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, sorbitan esters, alkyl sulfates, polysorbates and polyoxyethylene alkyl esters.

34. A method of Claim 33 wherein the alkalizing agent comprises tribasic sodium phosphate .

35. A method of Claim 34 wherein the alkalizing agent further comprises magnesium hydroxide.

36. A method of Claims 25 and 29 wherein

(a) the alkalizing agent comprises at least about 200 mg of tribasic sodium phosphate and at least about 100 mg of magnesium hydroxide; and

(b) the azithromycin comprises azithromycin multiparticulates, wherein said multiparticulates comprise

(i) azithromycin,

(ii) a mixture of glyceryl monobehenate, glyceryl dibehenate and glyceryl tribehenate, and

(iii) poloxamer 407.

37. A method of Claim 36 comprising contiguously administering to said human a single dose of an oral dosage form wherein said oral dosage form comprises:

(a) 300 mg to 400 mg of tribasic sodium phosphate;

(b) 200 mg to 300 mg of magnesium hydroxide; and

(c) multiparticulates, wherein said multiparticulates comprise

(i) azithromycin,

(ii) a mixture of glyceryl monobehenate, glyceryl dibehenate and glyceryl tribehenate, and

(iii) poloxamer 407,

and wherein said dosage form contains 1.5 gA to 4 gA of azithromycin.

38. A method of Claim 37 wherein the azithromycin comprises azithromycin dihydrate.

39. Azithromycin multiparticulates comprising:

(a) azithromycin;

(b) a surfactant; and

(b) a pharmaceutically acceptable carrier,

wherein at least 70% of the azithromycin is crystalline.

40. A multiparticulate of Claim 39 wherein said surfactant comprises a poloxamer and said carrier comprises a mixture of glyceryl monobehenate, glyceryl dibehenate and glyceryl tribehenate.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
URQUHART-DYKES & LORD
c/o Simpson, Alison
Attn. Fuller, Grover F. Jr.
30 Welbeck Street
London W1G 8ER
UNITED KINGDOM

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *(day/month/year)* 16/11/2004
Applicant's or agent's file reference 25240/700130	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/IB2004/001654	International filing date *(day/month/year)* 14/05/2004
Applicant PFIZER PRODUCTS INC.	

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 740.14.35

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Natalia Morancho Alcaine

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims,description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1*bis*(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43*bis*.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
25240/700130		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB2004/001654	14/05/2004	04/12/2003
Applicant		
PFIZER PRODUCTS INC.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 8 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      [ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [X] **Certain claims were found unsearchable** (See Box II).

3. [X] **Unity of invention is lacking** (see Box III).

4. With regard to the **title,**
   [X] the text is approved as submitted by ~~the~~ applicant.
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regards to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant.
      [ ] as selected by this Authority, because the applicant failed to suggest a figure.
      [ ] as selected by this Authority, because this figure better characterizes the invention.
   b. [X] none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2004/001654

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 21-37 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 21-37 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/001654

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 679 400 A (PFIZER) 2 November 1995 (1995-11-02) tables XIII,formulation,6	1-7,21, 22,24,30
X ✓	US 5 633 006 A (CATANIA JOSEPH S ET AL) 27 May 1997 (1997-05-27) examples 1-15	1,2,4,5
A	US 6 068 859 A (KORSMEYER RICHARD W ET AL) 30 May 2000 (2000-05-30) cited in the application the whole document	1

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 October 2004	[illegible] 2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Veronese, A

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Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/063838 A (JOHNSON BARBARA ALICE ; QUAN ERNEST SHING (US); PFIZER PROD INC (US)) 7 August 2003 (2003-08-07) page 5, line 11 - page 8, line 15 page 10, line 28 page 43, line 6 - page 44, line 6 page 47, lines 5-16 examples 1-6	38,39
X	WO 03/053399 A (JOHNSON BARBARA ALICE ; PFIZER PROD INC (US); FERGIONE MICHAEL BRUCE () 3 July 2003 (2003-07-03) examples 3-5	38
A	EP 0 298 650 A (PFIZER) 11 January 1989 (1989-01-11) the whole document	38

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB2004/001654

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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2004/001654	14.05.2004	04.12.2003

International Patent Classification (IPC) or both national classification and IPC
A61K9/16

Applicant
PFIZER PRODUCTS INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Veronese, A

Telephone No. +49 89 2399-7824

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 21-38 (IA)

because:

☒ the said international application, or the said claims Nos. 21-38 (IA) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 21-38 (IA)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6-20,22,23,25-29,31-38
	No:	Claims	1-5,21,24,30,39
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-40
Industrial applicability (IA)	Yes:	Claims	1-20,39,40
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III.

For the assessment of the present claims 21-38 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item IV.

The two following separate inventions have been identified:

Claims 1-37: pharmaceutical compositions comprising azithromycin and an alkalizing agent, and their use in relation to the treatment of gastrointestinal infections.

Claims 39-40: Multiparticulate pharmaceutical compositions comprising azithromycin in at least 70% crystalline form, a surfactant and a pharmaceutically active carrier.

These invention are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:
The problem to be solved by the present application is to provide pharmaceutical compositions for the treatment of microbial infections which cause reduced gastrointestinal side effects. As solution the inventors propose the preparation of compositions comprising azithromycin prepared according to the two inventions listed above.
Rule 13.1 PCT deals with the requirement of unity of invention, and states the principle that an international application should relate to only one invention or, if there is more than one invention, that the inclusion of those inventions in one international application is only permitted if all inventions are so linked as to form a single general inventive concept. Rule 13.2 PCT defines the method for determining whether the requirement of unity of invention is satisfied in respect of a group of inventions claimed in an international application. Unity of invention exists only when there is a technical relationship among the claimed inventions

involving one or more of the same or corresponding "special technical features." The expression "special technical features" is defined in Rule 13.2, as meaning those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art.
The problem underlying the present application has found similar solutions in the prior art: EP679400 (see the examples, and in particular example 12, table XII) discloses azithromycin compositions producing reduced gastrointestinal side effects (free from gastrointestinal drug-food interactions) which comprise azithromycin and the preferred alkaline agents of the present application (sodium triphosphate and sodium carbonate). In view of this prior art, the two inventions mentioned above are two separate inventions not linked by a single general inventive concept. In the present application no further technical feature(s) can be distinguished that can be regarded as a "special technical feature" involved in the technical relationship among the different inventions. Consequently, the present application lacks unity of invention in the sense of Art.13(1) PCT.

Since after invitation by the International Searching authority the applicant has paid one additional search fee, the subject matter of both the first and the second inventions has been searched and is object of the present opinion.

Re Item V.

1 The following documents have been cited in the search report. Where reference is made to them, the following numbering is used; unless otherwise indicated, reference is made to the relevant passages emphasized in the Search Report:

D1 : EP 0 679 400 A (PFIZER) 2 November 1995
D2 : US 5 633 006 A (CATANIA JOSEPH S ET AL) 27 May 1997
D3: US6068859
D4 : WO03/063838 A (PFIZER PROD INC (US)), 7 August 2003
D5: WO03/053399 (Pfizer), 3 July 2003

INVENTION 1

Novelty (Art.33(2) PCT)

D1 discloses (see the examples, and in particular example 12, table XII),

multiparticulate pharmaceutical compositions for oral use comprising azithromycin and the preferred alkaline agents of the present application (sodium triphosphate and sodium carbonate). These compositions produce reduced gastrointestinal side effects (they are free from gastrointestinal drug-food interactions).

D2 (see examples) discloses pharmaceutical compositions for oral use comprising azithromycin and an alkaline earth oxide (MgO in particular).

In view of this prior art, the subject matter of claims 1, 2, 3, 4, 5, 21, 22, 24, 30 may not be considered new in the sense of Art.33(2) PCT.

Inventive step (Art.33(3) PCT)

The subject matter of the first invention which is new differs from the prior art in that the oral compositions comprise additional components (like a behenate compound, or a poloxamer), or in that they comprise a specific dosage of azithromycin.
These additional technical features, however, do not appear to produce any new surprising technical effect. In the absence of any new effect, the subject matter of these claims is considered a trivial alternative of the prior art, and may not be considered to involve an inventive step in the sense of Art.33(3) PCT.

Industrial application

The subject matter of claims 1-20, is considered industrially applicable.
Claims 21-37 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

INVENTION 2

Novelty (Art.33(2) PCT)

D4 and **D5** (see the passages indicated in the search report) disclose the preparation of granulates comprising azithromycin in crystalline form (100% crystalline form), a surfactant (magnesium stearate and sodium laurate) and

pharmaceutically acceptable carriers. In view of this prior art, the subject matter of claim 39 is not new.

Inventive step (Art.33(3) PCT)

The subject matter of claim 40 differs from the prior art D4 and D5 in that a specific selection of surfactants has been selected (a mixture of glyceryl monobehenate, glyceryl dibehenate, and glyceryl tribehenate).
Substituting the surfactant of the prior art (magnesium stearate and sodium laurate) with the above mentioned mixture of surfactants does not however appear to produce any new surprising technical effect. Furthermore, D4 also mentions glyceryl behenate (see page 10, line 28) as an alternative to magnesium stearate. In the absence of any new effect, the subject matter of this claim is therefore considered a trivial alternative of the prior art, and may not be considered to involve an inventive step in the sense of Art.33(3) PCT.

Industrial application

The subject matter of claims 39 and 40 is considered industrially applicable.